

Research Article

An investigation of the relationship between autonomic dysreflexia and intrathecal baclofen in patients with spinal cord injury

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Objective: To study the relationship between autonomic dysreflexia and intrathecal baclofen in patients with spinal cord injury.

Design: Retrospective chart review.

Setting: Inpatient and outpatient acute rehabilitation facility.

Participants: Thirty-four subjects.

Interventions: We reviewed patients' medical records to ascertain the presence of symptomatic autonomic dysreflexia (AD) prior to and after implantation of an intrathecal baclofen (ITB) pump for spasticity in spinal cord injury patients. We recorded risk factors for autonomic dysreflexia including kidney and bladder stones, heterotopic ossification (HO), and ischial / sacral pressure ulcers.

Outcome Measures: Presence of autonomic dysreflexia pre and post-intrathecal baclofen pump placement, presence of risk factors associated with autonomic dysreflexia including (1) kidney or bladder stones, (2) heterotopic ossification, and (3) pressure ulcers.

Results: Of the 34 subjects, 25 (73.5%) experienced AD prior to ITB pump placement and only 2 (5.9%) after placement. Four subjects (11.8%) had kidney or bladder stones, of which, all had AD prior to placement and none had AD afterwards. Twenty-six subjects (76.5%) had pressure ulcers, of which, all experienced AD prior to placement and only one (0.02%) afterwards. Six patients (17.6%) had HO, of which 5 (83%) had AD prior to placement and none afterwards. Additionally, three patients (8.8%) had at least 2 of the above risk factors, of which, all had AD prior to ITB placement and none afterwards.

Conclusion: This study showed a significant reduction of symptomatic episodes of autonomic dysreflexia after spinal cord injury, even in those with additional risk factors for development of autonomic dysreflexia.

Keywords: Autonomic dysreflexia, Intrathecal, Baclofen

Introduction

Autonomic Dysreflexia (AD) affects 30–90% of those with chronic tetraplegia or high paraplegia¹ and 6% of patients in the acute phase (within 1 month) after initial spinal cord injury (SCI).² AD commonly occurs in those with SCI at or above T6 and manifests when a noxious stimulus below the level of injury is transmitted to the spinal cord through peripheral nerves. This stimulus triggers a surge in sympathetic activity from the abdominal splanchnic vasculature, causing wide-spread peripheral vasoconstriction, resulting in dangerously elevated blood pressure. To address the

hypertensive crisis, the brain sends inhibitory impulses to counteract the sympathetic overdrive, but these impulses are unable to be transmitted due to the spinal cord injury and blood pressures continue to remain elevated until the root cause is found. During some episodes, the reflex activity is quieted through re-positioning or medication administration without a precise underlying cause identified in each instance.

Reduction or prevention of AD episodes via modulation of the above series of events is also a potential approach to AD management. The best management of AD is likely prevention with appropriate management of bladder, bowel and skin.³ Common noxious stimuli that may trigger AD arise from insults to the bladder, bowel, skin or bone. AD is life-threatening

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due to risks of cerebral hemorrhage, myocardial infarction, and seizures, necessitating timely identification and management. Those with higher neurologic levels of injury and those with complete SCI by ASIA impairment scale exhibit more profound AD symptoms, and AD is three times more prevalent in tetraplegics with a complete injury versus an incomplete injury (91% complete vs 27% incomplete injuries).⁴ In our clinical practice the use of ITB to modulate spasticity in persons with SCI was noted to result in a reported reduction of AD episodes. The purpose of this study was to review a consecutive series of patients with SCI who received ITB and its relationship to AD episodes.

Methods

Study Design and Participants

A retrospective chart review was under-taken to study patients with SCI who were recipients of an intrathecal baclofen (ITB) pump for treatment of their spasticity. A total of 34 adult participants were included in the review. Mean age was 46 years, with a range from 23 to 81 years, with a mean time from initial SCI to pump implantation of 6 years with a range from 6 months to 10 years (Table 1). Our inclusion criteria included: age 18 years or greater and direct spinal cord injury due to trauma, spondylosis, or hematoma. One potential candidate was excluded due to a diagnosis of multiple sclerosis. Neurological level of injury (LOI) and ASIA impairment scale (AIS) characteristics are included in Table 2. All participants were patients at the MetroHealth Rehabilitation Institute of Ohio who had been seen in our SCI clinic. We reviewed their medical records to ascertain the presence of AD prior to and after implantation of an ITB pump for spasticity, based on documentation of our standard review of systems questions during clinic visits. We also recorded the presence of specific additional risk factors for AD in these patients including kidney/bladder stones,

heterotopic ossification (HO), and ischial/sacral pressure ulcers (Table 3).

Analysis

Standard descriptive statistics, such as means and frequencies, were used to characterize our study sample. To determine the association between AD and ITB a Related Samples McNemar test with a significance level of .05 was conducted. Due to our small sample size an exact test was used to determine significance level of the relationship between AD and ITB. Because the risk factor category sample sizes were very small (due to the small sample size of the study overall), we next used comparative analysis to create contingency tables for each category (AD episodes pre and post-ITB, presence of selected AD risk factor, etc) as seen in Table 3. The “product” function was utilized to compute percentages which allows for ease of reader understanding.

Results

Of the 34 subjects, 25 (73.5%) experienced AD prior to ITB pump placement and only 2 (5.9%) experienced AD after placement ($p < .001$) (Table 3). While there are a myriad of potential causes for AD events, we chose to include three common triggers of repeated AD episodes which were also included in our SCI Clinic template notes: kidney/bladder stones, HO, and sacral pressure ulcers. We felt that these also represented common triggers that would be present both pre and post-ITB placement for most patients, highlighting the effect of the addition of ITB in the presence of ongoing AD risk factors. In reviewing some of the risk factors for AD episodes (Table 3), we found that four subjects (11.8%) had kidney or bladder stones, of which, all had AD prior to placement and none had AD afterwards. Nine patients (26.5%) had pressure ulcers, of which, all experienced AD prior to placement and only one (11.1%) had AD afterwards. Six patients (17.6%) had HO, of which 5 (83%) had AD prior to placement and none had AD afterwards. Additionally, three patients (8.8%) had at least 2 of the above risk factors, of which, all had AD prior to ITB placement and none had AD afterwards. The presence of AD episodes was recorded from their

Table 1 Subject characteristics (n=34).

Characteristics	Number
Age (years): Mean/range	46/23–81
Sex	
Males	30
Females	4
Race/ethnicity	
White	22
Black	12
Tetraplegia/paraplegia	25/9
Complete/incomplete	18/16
Time (years) from SCI to ITB pump implant, Mean/range	6/0.5–10

Table 2 Number of patients with ITB pump by level of injury (LOI) and ASIA impairment scale (AIS) (n=34).

LOI	AIS A	AIS B	AIS C	AIS D	Total
Cervical	11	0	7	7	25
Thoracic	7	2	0	0	9
Total	18	2	7	7	34

Table 3 Analysis of AD before and after ITB, also incorporating selected risk factors of AD (n=34).

Patient Categories	Total Number of Possible Patients in Category	Number of Patients in Category	
AD Episodes pre-ITB	34	25	73.5%
AD Episodes post-ITB	34	2	5.9%
Positive history of stones	34	4	11.8%
Positive stone history plus AD episodes pre-ITB	4	4	100%
Positive stone history plus AD episodes post-ITB	4	0	0%
Positive history of pressure ulcers	34	9	26.5%
Positive pressure ulcer history plus AD episodes pre-ITB	9	9	100%
Positive pressure ulcer history plus AD episodes post-ITB	9	1	11.1%
Positive HO history	34	6	17.6%
Positive HO ulcer history plus AD episodes pre-ITB	6	5	83.3%
Positive HO history plus AD episodes post-ITB	5	0	0%
Positive history of 2 or more of the selected AD risk factors above	34	3	8.8%
Positive history of 2 or more of the selected AD risk factors above plus AD episodes pre-ITB	3	3	100%
Positive history of 2 or more of the selected AD risk factors above plus AD episodes post-ITB	3	0	0%

inclusion in standardized templated review of systems information in clinic notes. The post-ITB placement assessment period varied widely based on when patients had their ITB pumps placed, and ranged from 6 months to approximately 10 years.

Discussion

This study reveals that of 25 patients with SCI who were treated for spasticity with ITB, only 2 continued to experience AD post pump placement after a mean follow up period of 6.0 years. This review introduces the concept that the treatment of spasticity with ITB results in the reduction of AD episodes in persons with SCI, even in patients with multiple risk factors for the development of AD.

The relationship between intrathecal baclofen and autonomic dysfunction has not been well studied. Studies in animal models have shown that increased excitatory glutamatergic signaling to uninhibited motor neurons below the neurologic level of injury result in some degree of spasticity.⁵ Baclofen blocks

the release of these excitatory transmissions through GABA_B activation. Additionally, GABA_B activation has been linked to inhibition of detrusor over-activity in rats,⁶ which can be a cause of AD, especially when paired with detrusor-sphincter dyssynergia (DSD). GABA_A and GABA_B agonists have also been shown to improve DSD in rats.⁷ It may be through these mechanisms that Baclofen can reduce the incidence of AD.

Several case studies and one case series have looked at intrathecal baclofen and autonomic dysfunction. A case study of a patient with a T3 AIS B paraplegia whose severe AD episodes resolved after the spasticity was treated with ITB.⁸ This patient had a pump malfunction causing decreased baclofen flow into the intrathecal space, during which his AD episodes returned, but again resolved after adequate dosing was re-established. It is possible that significant spasticity itself, especially during severe acute spasms, may contribute to AD. A case series in brain injury patients with severe sympathetic storming and autonomic instability inadequately responsive to typical measures, showed improved autonomic function in 3 of 4 patients after treatment with ITB.⁹

In another case report, a patient with T5 AIS A paraplegia with spasticity and AD had complete sustained resolution of symptoms following ITB pump placement. However, his symptoms returned when the ITB pump had to be removed many months later due to mechanical failure.¹⁰ Long-term studies have also shown the positive effects of ITB on the quality of life in patients with SCI as this relates to a reduction of pain due to hypertonia and contractures, as well as improved urodynamics, bladder capacity, sphincter dyssynergia and continence.^{11,12}

Study Limitations

Our study limitations include retrospective chart review design, small sample size, and inconsistent time-frame for questioning regarding AD episodes post-ITB pump placement. Small sample size especially limits the ability to extrapolate to larger populations of patients, however, suggests a possible association is present and warrants further investigation. Future studies would benefit from specifically defined pre- and post-ITB pump placement intervals for assessment of AD episodes (ex. 6 months pre- and post-ITB placement). Consideration could be given to more elaborate methods of recording AD episodes as well as expanding the information obtained regarding each episode and likely underlying cause, if possible.

Conclusions

Though the benefit of ITB in satisfactory treatment of spasticity is known, our study highlights a possible association between ITB and reduction in AD symptomatology. There was a significant reduction in AD for at-risk patients with SCI, including those with additional risk factors commonly associated with the development of AD. Reduction and potentially prevention of AD episodes contributes to improved rehabilitation outcomes for our patients with SCI.

Disclaimer statements

Contributors None.

Funding None.

Conflict of interest None.

Ethics approval None.

References

- 1 Lindan R, Joiner E, Freehafer AA, Hazel C. Incidence and clinical features of Autonomic Dysreflexia in patients with spinal cord injury. *Paraplegia* 1980;18(5):285–92.
- 2 Krassioukov AV, Furlan JC, Fehlings MG. Autonomic dysreflexia in acute spinal cord injury: an under-recognized clinical entity. *J Neurotrauma* 2003;20(8):707–16.
- 3 Consortium for Spinal Cord Medicine. Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health care facilities. *J Spinal Cord Med* 2001;25 (Suppl 1):S67–88.
- 4 Curt A, Nitsche B, Rodic B, Schurch B, Dietz V. Assessment of autonomic dysreflexia in patients with spinal cord injury. *J Neurol Neurosurg Psychiatry* 1997;62(5):473–7.
- 5 Rabchevsky AG, Kitzman, PH. Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. *Neurotherapeutics* 2011;8(2):274–82.
- 6 Miyazato M, Sasatomi K, Hiragata S, Sugaya K, Chancellor MB, de Groat WC, *et al.* GABA receptor activation in the lumbosacral spinal cord decreases detrusor overactivity in spinal cord injured rats. *J Urol* 2008;179(3):1178–83.
- 7 Miyazato M, Yoshimura N, Nishijima S, Sugaya K. Roles of glycinergic and gamma-aminobutyric-ergic mechanisms in the micturition reflex in rats. *Low Urin Tract Symptoms* 2009;1(S1): S70–3.
- 8 Kofler M, Poustka K, Saltuari L. Intrathecal baclofen for autonomic instability due to spinal cord injury. *Auton Neurosci* 2009; 146(1–2):106–10.
- 9 Becker R, Benes L, Sure U, Hellwig D, Bertalanffy H. Intrathecal baclofen alleviates autonomic dysfunction in severe brain injury. *J Clin Neurosci* 2000;7(4):316–9.
- 10 Vaidyanathan S, Soni BM, Oo T, Hughes PL, Singh G, Mansour, P. Delayed complications of discontinuation of intrathecal baclofen therapy: resurgence of dyssynergic voiding, which triggered off autonomic dysreflexia and hydronephrosis. *Spinal Cord* 2004;42 (10):598–602.
- 11 Mertens P, Parise M, Garcia-Larrea L, Benneton C, Millet MF, Sindou M. Long-term clinical, electrophysiological and urodynamic effects of chronic intrathecal baclofen infusion for treatment of spinal spasticity. *Acta Neurochir Suppl* 1995;64:17–25.
- 12 Frost F, Nanninga J, Penn R, Savoy S, Wu Y. Intrathecal baclofen infusion: Effect on bladder management programs in patients with myelopathy. *Am J Phys Med Rehabil* 1989; 68(3):112–5.